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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,455	TANG ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-30 and 32-45* is/are pending in the application.

4a) Of the above claim(s) *32-34,37-40 and 42-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-30,35,36 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 21-30 and 32-45 are pending in the application.

[2] Applicants' amendment to the claims filed December 29, 2003 is acknowledged. This listing of the claims replaces all prior versions and listings of the claims of the instant application.

[3] Applicants' amendment to the specification filed December 29, 2003 is acknowledged.

[4] Receipt of a Declaration, filed December 29, 2003, is acknowledged.

[5] Applicant's arguments filed December 29, 2003 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

[7] Receipt of an information disclosure statement filed December 29, 2003 is acknowledged.

Lack of Unity

[8] Applicants' request for rejoinder of claims 21-22 and 35-36 is acknowledged. In view of the amendment to the claims, filed December 29, 2003, claims 21-22 and 35-36 are rejoined and have been co-examined with the claims of elected Group XX. The amended claims are drawn to a polypeptide that corresponds to the polynucleotide of elected Group XX and thus, the claimed inventions share a corresponding special technical feature.

Rejoinder

[9] Applicants' request for rejoinder of claims 32-34 and 39-40 as being drawn to methods of using the polynucleotide of Group XX is acknowledged. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Until an elected product claim is found allowable, an otherwise proper

restriction requirement between product claims and process claims may be maintained. However, as the claims of Group XX are not yet allowable for the reasons stated below, rejoinder is not yet required. If the polynucleotide of Group XX is found to be allowable, withdrawn claims will then be evaluated for rejoinder according to MPEP § 821.04.

[10] It should be noted that withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. Currently, claims 32-33 and 40 are not commensurate in scope with the claimed polynucleotide of Group XX.

[11] Claims 32-34, 37-40, and 42-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

[12] Claims 21-30, 35-36, and 41 are being examined on the merits.

Specification/Informalities

[13] In view of applicants' amendment to the specification, the objection to the specification as set forth at item [7] of the Office action mailed September 23, 2003 is withdrawn.

[14] The objection to the specification as set forth in item [8] of the Office action mailed September 23, 2003 is maintained. The specification is objected to as being confusing in that the specification teaches the polypeptide of SEQ ID NO:6, encoded by SEQ ID NO:22, is a hydrolase protein (see e.g., pages 1 and 20-22 of the specification), while also asserting the polypeptide of SEQ ID NO:6 is homologous to a phospholipase A2 inhibitor (see page 62 of the specification). Is the specification indicating that the polypeptide of SEQ ID NO:6 has the dual function of both a hydrolase and a hydrolase inhibitor? Based on these contradictory teachings, it is unclear as to the function of the polypeptide of SEQ ID NO:6. Applicants have not responded to and therefore do not dispute the instant objection. It is suggested that applicants clarify the contradictory disclosure. See MPEP §§ 608.01 and 702.01.

Claim Rejections - 35 USC § 101

[15] The rejection of claims 21-30, 35-36, and 41 under 35 U.S.C. 101 as set forth in item [10] of the Office action mailed September 23, 2003 is maintained for the reasons of record and the reasons stated

below. It is the examiner's position that the asserted utilities for the claimed polynucleotide, polypeptide, and microarray are neither substantial nor specific. Applicants traverse the instant rejection by arguing that the claimed polynucleotide has utility without requiring knowledge of the function of the encoded polypeptide. Applicants cite the Declaration of Dr. Tod Bedilion filed December 29, 2003 (hereafter referred to as the "Bedilion Declaration") in support of their argument and assert that the Bedilion Declaration demonstrates the utility rejection is without merit. Applicants assert the Bedilion Declaration describes how the claimed polynucleotide can be used in gene expression monitoring systems that were allegedly well known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Applicants assert that the law has never required knowledge of biological function to prove utility and further assert the uses of the polynucleotide in gene expression monitoring applications are independent of its biological function. Applicants' argument is not found persuasive.

It is noted that Dr. Tod Bedilion is a consultant for Incyte Corporation and thus is a concerned party. Regarding the merit of the examiner's position, *any* polynucleotide can be used for gene expression monitoring and consequently, this asserted utility is *not* specific. Furthermore, the specification fails to provide guidance as to enable a skilled artisan to use data relating to the claimed polynucleotides derived from the results of toxicology testing and what the results would mean. For example, if the claimed polynucleotide was attached to a microarray and used in toxicology testing or gene expression analysis and a result showed that expression was increased when a cell was treated with a particular agent, the specification provides no basis on which a skilled worker would be able to determine whether that result is meaningful. As such, further experimentation would be required to interpret the results of such gene expression analysis and consequently, this asserted utility is *not* substantial. The examiner acknowledges that the utility requirement does not require knowledge of biological function. A claimed polynucleotide can meet the requirements of utility as long as the specification discloses a credible, specific and substantial asserted utility or a well-established utility for the claimed polynucleotide, even though the function of the polynucleotide or encoded polypeptide is not disclosed in the specification. For example, Shattuck-Eidens et al. (US Patent 5,693,473) teach mutant alleles of the *BRCA1* gene that

predispose a patient to developing breast and ovarian cancers (abstract). While there is no disclosure of the function of the mutant *BRCA1* genes or their gene products, the invention nevertheless has utility as being an indicator for susceptibility to developing breast and ovarian cancers. Contrary to this example, the instant specification fails to assert a specific and substantial utility for the claimed polynucleotide.

Applicants argue that in order to satisfy the utility requirement of 35 USC 101 and 112, first paragraph, the applicant need only show that the invention is "practically useful" and confers a "substantial", "specific benefit" on the public. Applicants cite the following case law that is allegedly relevant to the instant rejection: *Anderson v Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973); *Brenner v Manson*, 383 US 519, 534-35, 148 USPQ 689 (1966); *Juicy Whip Inc. v Orange Bang Inc.*, 51 USPQ2d 1700 (Fed Cir 1999); *Stiftung v Renishaw PLC*, 945 F2d 1173, 1180, 20 USPQ2d 1094 (Fed Cir 1991); *Standard Oil Co. v Montedison, S.p.a.*, 212 USPQ 327 343 (3d Cir 1981); *Cross v Izuka*, 753 F2d 1040, 1048 (Fed Cir 1985); *Nelson v Bowler*, 626 F2d 853, 856, 206 USPQ 881 (CCPA 1980); *In re Cortright*, 165 F3d 1353, 1357, 49 USPQ2d 1464 (Fed Cir 1999); *In re Brana*, 51 F3d 1560, 1566; 34 USPQ2d 1436 (Fed Cir 1995); and *In re Langer*, 503 F2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). Applicants' argument is not found persuasive. The essential disagreement between the examiner's position and applicants' position appears to be the interpretation of what constitutes a specific and substantial utility, as will be explained in detail below.

Applicants argue the claimed invention meets all necessary requirements for establishing a credible utility under the law as there are allegedly "well-established" uses for the claimed invention and there are allegedly specific practical and beneficial uses disclosed in the specification for the claimed invention as disclosed in the Bedilion Declaration and that objective evidence, allegedly not considered by the Office, further corroborates the credibility of the asserted utilities. Applicants' argument is not found persuasive.

The claimed invention has no well-established use and there is no specific and substantial use for the claimed invention. Each of applicants' asserted utilities for the claimed polynucleotide, *i.e.,* diagnosis of conditions and disorders characterized by expression of HYDRL, for toxicology testing, and for drug discovery, will be addressed in detail below. Applicants do not elaborate on the "objective evidence" that

has allegedly not been considered by the Office. Contrary to applicants' assertion, the examiner has fully considered ALL evidence of record in evaluating the claims for utility under 35 USC §§ 101 and 112, first paragraph.

Applicants argue the claimed invention has real-world utility as allegedly being useful for toxicology testing, drug development, and disease diagnosis through gene expression profiling, allegedly explained in the Bedilion Declaration, the substance of which is allegedly not rebutted by the Examiner. Applicants argue there is no dispute that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Applicants assert that these uses are sufficient to establish utility for the claimed polynucleotide. Applicants argue the Bedilion Declaration explains the many reasons why a person skilled in the art reading the instant application would have understood this application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. Applicants argue the examiner does not address the "fact" that the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotide. Applicants argue that the claimed invention is not some random sequence whose value as a probe is speculative or would require further research to determine. Applicants' arguments are not found persuasive.

It should be noted that the Bedilion Declaration has only been made of record with the amendment filed December 29, 2003 and therefore, the examiner has not had the opportunity to rebut the statements provided therein. The examiner agrees with the Bedilion Declaration to the extent that *any* polynucleotide, including the claimed polynucleotide, can be included as part of a cDNA microarray, however, this use does not confer patentable utility on the claimed polynucleotide as this utility is considered a general use and not a utility that is specific and substantial. MPEP § 2107.01 states, "A 'specific utility' is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention". Expressed polynucleotides have a variety of general uses, *e.g.,* as a probe for hybridization or as a template for protein expression – these uses are applicable to

any expressed polynucleotide and are not specific to the claimed polynucleotide. Also, the claimed polynucleotide has no substantial utility. MPEP § 2107.01 states, "Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities". Because the specification fails to provide guidance to allow a skilled artisan to use data relating to the claimed polynucleotide derived from the results of gene expression analysis and what the results would mean, the results of gene expression monitoring assays would be meaningless without further research. In this case, the asserted use of the claimed polynucleotide for gene expression monitoring would be an assay to measure a polynucleotide that itself has no specific and substantial utility. MPEP § 2107.01 states that this utility is *not* substantial: "A method of assaying for or identifying a material that itself has no specific and/or substantial utility". Consequently, the claimed polynucleotide has no specific and substantial utility.

Applicants argue that because the claimed polynucleotide is expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Applicants cite case law as allegedly relevant to the patentable utility of research tools.

It is true that a scale, gas chromatograph, screening assays, and nucleotide sequencing techniques have utility as research tools. However, such tools present a result that requires no further experimentation for interpretation, *e.g.*, a scale provides the weight of an object and requires no further experimentation for interpretation of the result. In the instant case, a more representative analogy to the claimed polynucleotide would be that of a scale without an identifiable unit of measure – one could place an object on the scale, however, further experimentation would be required to interpret the result and determine the weight of the object. Similarly, as applicants have provided no information regarding altered expression of the claimed polynucleotide or guidance for interpreting the results of gene expression analysis, additional experimentation would be required to interpret a result obtained using the claimed polynucleotide for gene expression analysis.

Applicants argue there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative gene expression including understanding the effects of a potential drug for treating various disorders. Applicants argue that, since the specification discloses the

claimed polynucleotide to be expressed in normal and cancerous cells and expresses a protein that is allegedly a member of a class of proteins known to be associated with various diseases, there can be no dispute that an ordinarily skilled artisan could put the claimed invention to such use, i.e., derive more information about relative gene expression than without it. Applicants' arguments are not found persuasive.

There is no evidence of record to suggest that the claimed polynucleotide has ANY association with ANY disease state. Applicants are invited to provide such evidence. However, in view of the lack of such evidence, such an association between the claimed polynucleotide and the stated disease states, *e.g.,* altered expression or polymorphism, does not exist. As stated above, any polynucleotide can be used for gene expression analysis and the specification fails to provide guidance to allow a skilled artisan to use information relating to the claimed polynucleotide derived from the results of gene expression analysis and what the results would mean, the results of gene expression monitoring assays using a cDNA microarray comprising the claimed polynucleotide would be meaningless without further research. In this case, the asserted use of the claimed polynucleotide for gene expression monitoring would be an assay to measure a polynucleotide that itself has no specific and substantial utility. MPEP § 2107.01 states that this utility is *not* substantial: "A method of assaying for or identifying a material that itself has no specific and/or substantial utility". Consequently, the claimed polynucleotide has no specific and substantial utility.

Applicants refer to Dr. Bedilion's opinionated discussion of Brown et al. (US Patent 5,807,522, cited by applicants). Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. Applicants also cite the references of Rockett et al. (*Xenobiotica* 29:655) and Lashkari et al. (*Proc Natl Acad Sci* 94:8945-8947) as allegedly describing the use and importance of gene expression technology with respect to drug screening and toxicology testing. Applicants' arguments are not found persuasive.

The claims of the Brown et al. patent are drawn to methods of forming microarrays (see, for example, claim 1 of Brown et al.). Methods of forming a microarray have patentable utility. However, in

the instant case, a microarray comprising the claimed polynucleotide does not have patentable utility as stated in detail above. Applicants' arguments and alleged supporting evidence merely indicate that microarray technology is important and useful to the scientific community. These publications are unrelated to the claimed polynucleotide and fail to demonstrate the claimed invention has *any* patentable utility. The use of the claimed and functionally uncharacterized polynucleotide in such studies would provide no more information than the use of any other uncharacterized polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide as stated above. Furthermore, due to the lack of disclosure of a correlation between the claimed polynucleotide and a particular disorder or guidance for interpreting the data obtained from gene expression analysis, the asserted utility is also not substantial, as discussed in detail above.

Applicants argue the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Applicants cite the references of Rockett et al. (*Xenobiotica* 29:655), Nuwaysir et al. (*Mol Carcinogen* l24 :153-159), Steiner et al. (*Tox Lett* 13 :467-471), Rockett et al. (*Environ Health Perspectives* 107:681), and an email from Dr. Cynthia Afshari to an Incyte employee, and examples (as set forth at the bottom of page 20 of the response filed December 29, 2003) that allegedly support applicants' assertions. Applicants argue that, because the examiner has allegedly failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and disease diagnosis, the rejections should be withdrawn. Applicants' arguments are not found persuasive.

Each of these uses (toxicology testing, drug development, and disease diagnosis) will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, applicants argue that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention therefore possesses patentable utility. However, for a utility to be "well-established" it must be specific, substantial and credible. In this case all expressed polynucleotides have use in gene expression monitoring for toxicology testing and consequently, this utility is not specific. Furthermore, the specification fails to disclose the methods and information necessary for a skilled artisan to use the claimed polynucleotide for toxicology

testing, *e.g.,* how would one interpret the results obtained from such testing? Therefore, this is a utility that would apply to virtually every member of a general class of materials, such as any collection of expressed polynucleotides. Such a utility is *not* specific and does *not* constitute a "well-established" utility. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gleaned from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility that would apply to virtually every member of a general class of materials, such as any collection of polynucleotides. Even assuming *arguendo* that the expression of applicants' claimed polynucleotide was affected by a test compound in an array for drug screening, the specification does not disclose any guidance for interpretation of the result, and none is known in the art. Given this consideration, the claimed polynucleotide has no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information generated using this nucleic acid may have.

With regard to drug discovery and development, applicants mention gene expression profiling as one use of the claimed polynucleotide. Applicants refer to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, applicants are incorrect in asserting that the efficacy (ability to produce a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual "hit" obtained from this procedure. The first requirement is that one must know the biological significance of the polynucleotide(s) which is/are being evaluated. Without this information, the results of the transcript image are useless because one would not inherently recognize how to interpret the result of increased or decreased polynucleotide expression or even what significance could be attributed to such changes in expression profiles. As such information has not been provided in the specification, further experimentation is required to identify a "real world" use for the claimed polynucleotide.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is

derived from normal or cancerous cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed polynucleotide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be specifically associated in some way with the molecule. In the absence of any disclosed relationship between the claimed polynucleotides or encoded proteins and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself.

Applicants argue they have demonstrated that the polypeptide of SEQ ID NO:6 is a member of the leucine-rich repeat family and cite Table 2 in the specification as providing such evidence. Applicants argue O'Donnell et al. (*J Leuk Biol* 72:478-485) corroborates their assertion that SEQ ID NO:6 and encoding polynucleotides may be useful in the diagnosis and treatment of immune disorders. Applicants' argument is not found persuasive.

Below is the information for SEQ ID NO:6 listed in Table 2 of the specification, which applicants allege demonstrates that SEQ ID NO:6 is a member of the leucine-rich repeat family.

6	347	S39 S274 S323	N79 N186 N269 N306 N325	Leucine rich repeat domains: K93-A140, T141-T188, L189-P236, D237-G284 Signal peptide: M1-A35	Phospholipase A2 inhibitor [Agkistrodon blomhoffii siniticus] (GI 3358089)

Applicants disclosure that SEQ ID NO:6 includes leucine-rich repeat domains is sufficient to suggest that SEQ ID NO:6 belongs to the family of leucine-rich repeat proteins. However, it is noted that members of this protein family are structurally and functionally diverse (see, *e.g.,* Enkhbayar et al. *Proteins* 54:394-403) and mere inclusion of a protein within a protein family based on a common structural feature in no way provides evidence that the claimed polynucleotide is useful in treating ANY disorder – particularly immune disorders and the specification fails to provide guidance for using the claimed polynucleotide to diagnose or treat any such disorder. It should be noted that the specification states that, in addition to immune disorders, the claimed polynucleotide is useful in diagnosing hundreds of other diseases and disorders (see pages 42-44 of the specification). It should also be noted that the specification provides

conflicting information regarding the function of SEQ ID NO:6 and consequently, further research would have been required to determine the biological significance of the claimed polynucleotide. For example, additional information is provided for SEQ ID NO:6 in Table 2 (see Table 2 excerpt above) indicates that the protein is a phospholipase A2 inhibitor, while the specification asserts the polypeptide has hydrolase activity as the specification discloses the "[i]nvention relates to nucleic acid and amino acid sequences of hydrolase proteins" (page 1, line 4 of the specification).

Applicants argue that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, applicants state that such a showing of actual use or commercial success is conclusive proof of utility. Applicants argue that a vibrant market has developed for databases containing all expressed genes, including those of Incyte, the real party at interest. Applicants state Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Applicants' arguments are not found persuasive.

The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. Many products that lack patentable utility enjoy commercial success, are used, and are considered valuable, *e.g.,* a pet rock. In this case, applicants' asserted utilities are neither substantial or specific. Furthermore, while applicants present evidence showing that the database is commercially valuable, there is no evidence to suggest that the database is any more or less valuable with the inclusion of the *claimed* polynucleotide.

Applicants argue that, rather than responding to the evidence allegedly demonstrating utility, the examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the clamed polynucleotides are not "specific and substantial asserted" utilities. Applicants argue the examiner is incorrect both as a matter of law and as a matter of fact. Applicants' arguments are not found persuasive.

It is the examiner's position that the claimed invention has no well-established use and there is no specific or substantial use for the claimed invention, even after FULL consideration of the "evidence" as provided in the specification. Applicants' arguments will be addressed in detail below.

Applicants argue that the examiner's rejection is based on the grounds that, without information as to the biological role of the claimed polynucleotide, the claimed invention lacks specific patentable utility. Applicants argue that, according to the examiner applicants are required to provide a specific and substantial interpretation of the results generated in an expression analysis. Applicants argue that specific and substantial interpretations regarding biological function are not necessary for obtaining a US patent. Applicants state the relevant question is not how or why the invention works, but whether the invention provides an "identifiable benefit" in currently available form. Applicants argue that the present invention meets this test. Applicants argue that the threshold for patentable utility is low and that only throwaway utilities are insufficient. Applicants' arguments are not found persuasive.

It is noted that applicants' arguments have mischaracterized the examiner's position. The examiner has fully considered applicants' "evidence" allegedly demonstrating utility and, in accordance with 35 USC § 101 has determined the claimed invention to lack patentable utility as the asserted utilities are neither specific nor substantial. The rejection never states that the precise biological role of a polynucleotide is required for it to possess patentable utility. The examiner acknowledges applicants' assertion that biological function of a polynucleotide need not be disclosed for a claimed polynucleotide to have patentable utility (see the example of Shattuck-Eidens et al. in US Patent 5,693,473 as described above). However, the specification fails to provide sufficient guidance such that one of ordinary skill in the art can use the claimed polynucleotide as a disease marker or for toxicology testing, drug discovery, or disease diagnosis and as such, there is no specific and substantial asserted utility. For example, if the claimed polynucleotide were used in a microarray for toxicology testing and if a compound caused the claimed polynucleotide to be expressed at a decreased level as demonstrated by the data generated using the microarray, what information does this provide, other than to initiate further experimentation? In view of the specification, a skilled artisan would recognize that the determination of whether a compound is potentially therapeutic or deleterious requires significant further research, and thus the asserted utility is

not substantial. Also, *any* expressed polynucleotide *can* be used in a microarray – just as any polynucleotide can be used for protein expression and thus the asserted utility is also not specific.

Applicants allege the examiner has refused to impute the utility of the members of the leucine-rich repeat (LRR) family of proteins to HYDRL-6 (SEQ ID NO:6). Applicants argue the examiner takes the position that utility of the claimed polynucleotide cannot be imputed unless applicants identify which particular biological function within the class of LRR proteins is possessed by HYDRL-6. Applicants argue the examiner would require that all LRR proteins possess a "common" utility in order to demonstrate utility by membership in a class. Applicants state the case law requires only that the class not contain a substantial number of useless members. Applicants argue the examiner has treated HYDRL-6 as if it was in a general class of all polynucleotides, rather than the LRR family of proteins. Applicants argue the examiner has not presented any evidence that the LRR family of proteins has any, let alone a substantial number, of useless members. Applicants argue that even if the examiner's common utility criterion were correct, the LRR family would meet it as members of the LRR family closely related to SEQ ID NO:6 are allegedly involved in immune response and cell adhesion. Applicants argue the person of ordinary skill in the art allegedly does not need to know anything more about the claimed invention in order to be able to use it and the Office action presents no evidence to the contrary. Applicants argue the examiner concludes that a skilled artisan would need to confirm the activity of a given LRR protein and that HYDRL-6 is useful only for further study of HYDRL-6. Applicants argue that knowledge that HYDRL-6 is a leucine-rich glycoprotein is sufficient to make it useful for diagnosis and treatment of cell proliferation, immune system, genetic, and neurological disorders. Applicants argue HYDRL-6 has been shown to be expressed in gastrointestinal, reproductive, hematopoietic/immune, and cardiovascular tissues and in tissues associated with cancer or inflammation. Applicants conclude that these facts must be accepted as true in the absence of evidence or sound scientific reasoning to the contrary. Applicants' arguments are not found persuasive.

Based upon applicants' disclosure (see excerpt from Table 2 above) it would appear that HYDRL-6 has leucine-rich repeats, which are allegedly characteristic of members of leucine-rich repeat proteins. While applicants assert that all members of the LRR protein family have utility, applicants fail to assert a

specific and substantial utility or a well-established utility for all LRR members and there is no evidence of record for a utility that is well-established or is specific and substantial for all LRR protein members. Members of the LRR family have a broad and diverse array of structures and functions, and thus, contrary to applicants' assertion, no single utility would apply to all members of the class. For example, Enkhbayar et al. (*Proteins* 54:394-403) teach "LRRs are present in over 2000 different proteins... ...have been identified in viruses, bacteria, arcaea, and eukaryotes... ...include hormone receptors, tyrosine kinase receptors, cell-adhesion molecules, bacterial virulence factors, enzymes, and extracellular matrix-binding glycoproteins" (page 394, left column, middle). Applicants are invited to demonstrate evidence of a well-established utility or a specific and substantial utility that would apply to all LRR family members. Applicants argue that SEQ ID NO:6 is closely related to the proteins of O'Donnell et al. and Saito et al. and therefore, one of ordinary skill in the art would not require further knowledge of its function. However, it is noted that the references of O'Donnell et al. and Saito et al. were published after the filing date of the instant application and were not available to a skilled artisan at the time of the invention. It should also be noted that the specification provides conflicting information regarding the function of SEQ ID NO:6 and consequently, further research would have been required to determine the biological significance of the claimed polynucleotide. For example, additional information is provided for SEQ ID NO:6 in Table 2 (see Table 2 excerpt above) indicates that the protein is a phospholipase A2 inhibitor, while the specification asserts the polypeptide has hydrolase activity as the specification discloses the "[i]nvention relates to nucleic acid and amino acid sequences of hydrolase proteins" (page 1, line 4 of the specification). Even assuming *arguendo* that one of ordinary skill in the art could have used the claimed polynucleotide for diagnosing and/or treating a disease – which one cannot – one of ordinary skill in the art would have recognized the necessity of determining which of the asserted functions – if SEQ ID NO:6 has any function as it is just as likely that it is non-functional – belongs to SEQ ID NO:6 in order to diagnose or treat a particular disease. There is no evidence of record that the claimed polynucleotide is involved in ANY disease state and it is just as likely that it is not. In view of the failure of the specification to provide a correlation of the claimed polynucleotide to a specific disease state and the necessary guidance for using the claimed polynucleotide to diagnose and treat a specific disorder, significant further research would be

necessary for the skilled artisan to use the claimed polynucleotides in a real world context, and thus the asserted utility is not substantial.

Applicants argue the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Applicants state that only a limited subset of research uses are not substantial: those in which the only known use for the claimed invention is to be an object of further study, thus merely inviting further research. Applicants argue that nowhere in their cited case law is it stated or implied that a material cannot be patentable if it has some other, additional beneficial use in research. Applicants argue the claimed invention has a beneficial use in toxicology testing, drug discovery, and disease diagnosis. Applicants argue the claimed polynucleotide is a tool not an object of research. Applicants argue the data generated as a result of gene expression monitoring using the claimed invention is not merely to study the polynucleotide itself, but to study properties of tissues, cells, and potential drug candidates and toxins. Applicants argue that without the claimed invention, information regarding properties of tissues, cells, and potential drug candidates and toxins is less complete. Applicants argue the invention has numerous additional uses as a research tool including diagnostic assays, chromosomal markers, ligand screening assays and drug screening.

As discussed above, whereas a scale or gas chromatograph has patentable utility as a research tool as providing a result that can be readily used and provides a specific benefit in currently available form, in this case, the claimed polynucleotide does NOT provide a specific benefit in currently available form and the asserted uses of the claimed polynucleotide either apply to the general class of polynucleotides (chromosomal marker) and/or would require further experimentation as described above (diagnostic assay, ligand screening assay, and drug screening). The claimed polynucleotide is not disclosed as having a property that can be identifiably and specifically useful without further, additional experimentation. The claimed invention is, in fact, the object of further study, merely inviting further research. For example, the specification provides no guidance to allow a skilled artisan to use data relating to the claimed polynucleotide derived from the results of toxicology testing and what the results would mean. For example, if the claimed polynucleotides were attached to a microarray and used in toxicology testing or gene expression analysis and a result showed that expression was increased when

a cell was treated with a particular agent, the specification provides no basis on which a skilled worker would be able to determine whether that result is meaningful. As such, further experimentation would be required to interpret the results of such gene expression analysis. Contrary to applicants' assertions, none of the asserted utilities for the claimed polynucleotide is specific and substantial.

Applicants challenge the legality of the Patent Examination Utility Guidelines. Applicants argue that "unique" or "particular" utilities have never been required by the law and applicants are unaware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Applicants argue that to meet the utility requirement, the invention need only by "practically useful" and confer a "specific benefit" on the public. Applicants' arguments are not found persuasive.

Regarding the Training Materials, applicants are reminded that the examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the examiner has no authority to disregard such guidelines or to apply his own interpretation of patent law in the examination of the application. Furthermore, as set forth in the guidelines and the MPEP, the guidelines were promulgated by the Patent Office in accordance with all applicable case law and thus are believed to be consistent therewith. Applicants are further reminded that the examiner has no authority to comment in regard to the legality of the new utility guidelines or the MPEP as set forth by the USPTO. Accordingly, it is the examiner's position that the instant claims, based on an analysis of the utility requirement of 35 USC § 101 and following the current Utility Guidelines, have no specific, substantial, or credible utility.

Regarding applicants' comments regarding a "unique" utility, it is noted that applicants' characterization of the examiner's position is somewhat misleading. Applicants have never been asked to identify a utility that is unique, i.e., not shared by any other compounds or compositions. Rather, applicants have been required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention. An invention certainly can have a utility that is shared by other compounds or compositions. While a utility need not be unique to

a claimed invention, it must nonetheless be specific, and in currently available form, in order to satisfy 35 USC § 101.

Claim Rejections - 35 USC § 112, Second Paragraph

[16] In view of the amendment to the claims filed December 29, 2003, the rejection of claims 23, 26-28, 30, and 41 under 35 U.S.C. 112, second paragraph, as set forth at item [11] of the Office action mailed September 23, 2003 is withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

[17] The written description rejection of claims 21, 23, 26-28, 30, 35, 41, and 43-45 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [12] of the Office action mailed September 23, 2003 and for the reasons stated below.

It is the examiner's position that the claimed genera of polynucleotides, polypeptides, and microarrays are not adequately described in the specification. Applicants argue the claimed subject matter is either disclosed or is conventional or well known to a skilled artisan. Applicants provide alleged support for the variants and fragments as encompassed by the claims. Applicants argue that a skilled artisan would recognize polypeptide sequences that are naturally occurring variants that are at least 90% identical to a nucleic acid encoding SEQ ID NO:6 or the nucleic acid of SEQ ID NO:22. Applicants argue that given a naturally occurring polypeptide sequence, it would be routine for a skilled artisan to recognize whether it is a variant of a nucleic acid encoding SEQ ID NO:6 or the nucleic acid of SEQ ID NO:22. Based on this alleged "routine recognition", applicant concludes that the specification provides an adequate description of the claimed variants of a nucleic acid encoding SEQ ID NO:6 or the nucleic acid of SEQ ID NO:22. Applicant's argument is not found persuasive.

The specification provides only *a single representative species* of the claimed genus of polynucleotides, *i.e.,*, SEQ ID NO:22 and genus of claimed polypeptides, *i.e.,* SEQ ID NO:6. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to

practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Other than the *single representative species* as described above, the specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of polynucleotides encompasses species that bind to polypeptides that are widely variant in both structure and function, including (but not limited to) functional and non-functional allelic variants and polypeptides having function other than hydrolase or phospholipase A inhibitory activity (whichever activity is exhibited by SEQ ID NO:6 as the specification is sufficiently confusing such that the examiner cannot identify which activity is intended for SEQ ID NO:6). As such, the disclosure of the single representative species of SEQ ID NO:22 or SEQ ID NO:6 is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus. Applicant's alleged supporting description of variants of a nucleic acid encoding SEQ ID NO:6 or the nucleic acid of SEQ ID NO:22 merely provides a textual description of said variants without providing any structural or functional features of the species encompassed by the genus. As such, a skilled artisan would *not* be able to visualize the structure of each member of the claimed genus. Furthermore, because there is no functional limitation provided for the variants of a nucleic acid encoding SEQ ID NO:6 or the nucleic acid of SEQ ID NO:22, one of skill in the art would recognize that the claimed genus of variants encompasses species having substantial variation of function within the genus. One of skill in the art would recognize that such variants encompass polypeptides having *any* activity, including non-functional

polypeptides and polypeptides having a function other than hydrolase or phospholipase A inhibitory activity (whichever of these is the intended activity). When there is substantial variation within a genus, as is the instant case, one must describe a sufficient variety of species to reflect the variation within the genus. The single representative species of SEQ ID NO:22 or SEQ ID NO:6 fails to describe the entire genus of claimed polynucleotides or polypeptides, respectively.

Applicant summarizes case law citing *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed Cir 1993) and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed Cir 1997) as court cases in which the recitation of functional characteristics of a DNA, without description of structural features has been a basis by which the courts have found invalid claims to DNA. Applicant argues the claims at issue are in contrast to the claims of the *Lilly* and *Fiers* cases as applicant alleges the claimed genus of polynucleotides is defined by structure rather than function. Applicant argues there is no reliance solely on functional characteristics of the claimed polynucleotides. Applicant argues the Office has failed to base the written description inquiry "on whatever is now claimed" and fails to provide an appropriate analysis of the instant claims and how they differ from those of the *Lilly* and *Fiers* cases. Applicant's arguments are not found persuasive.

While it is acknowledged that the current claims differ from those of the *Lilly* and *Fiers* cases, as discussed in the written description Guidelines and MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicants were in possession of the claimed genus. A representative number of species means that the species that are adequately described are representative of the entire genus. The specification discloses only a single representative species of the claimed genus of claimed polynucleotides, i.e., SEQ ID NO:22 and only a single representative species of the claimed genus of claimed polypeptides, i.e., SEQ ID NO:6. Furthermore, as stated above, there is substantial variation within the structure AND function of the genus of claimed polynucleotides and polypeptides. When there

is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of the invention, one of skill in the art would recognize the absence of the ability to predict the function(s) of all species of polynucleotides and polypeptides encompassed by the genus. For inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus. As described above, one of skill in the art would recognize that the genus of variants of a nucleic acid encoding SEQ ID NO:6 or the nucleic acid of SEQ ID NO:22 or the genus of variants of SEQ ID NO:6 encompasses species having *substantial* variation of both structural AND functional features. As such, neither the description of the structure and function (either hydrolase or phospholipase A2 inhibitory activity) of SEQ ID NO:6 nor the disclosure of solely structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus of claimed polynucleotides and polypeptides.

Applicants argue the claims do not describe a genus that is highly variant. Applicant argues that available evidence indicates that the claimed genus is of narrow scope. In support of applicant's assertion, they rely on the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078; cited by applicant). Applicants argue that, based on the teachings of Brenner et al., naturally-occurring molecules may exist that could be characterized as leucine-rich glycoproteins with only 40% identity over 70 amino acid residues of SEQ ID NO:6. Applicant argues the claims recite, e.g., a naturally occurring amino acid sequence with at least 90% identity to SEQ ID NO:6, which has 347 amino acids. Applicant asserts this variation is far less than those leucine-rich glycoproteins having as little as 40% identity over 70 residues of SEQ ID NO:6. Applicants' argument is not found persuasive.

Applicant improperly attempts to apply the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) to support their argument. Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) clearly state that their comparisons "have been assessed using proteins whose relationships are known reliably from their [three dimensional] structures and functions, as described in the SCOP database" (page 6073, abstract). Murzin et al. (*J Mol Biol* 247:536-540) teach that the proteins of the SCOP database have been characterized both in their three dimensional structures AND their function. In the instant case, there is no

evidence of record that would indicate that the polypeptide of SEQ ID NO:6 has been characterized by either of these methods. In fact, the function of the polypeptide of SEQ ID NO:6 appears to have been assigned based solely on its amino acid sequence – not on its three dimensional structure or its alleged hydrolase or phospholipase A2 function. The specification provides no disclosure of the three dimensional structure of the polypeptide of SEQ ID NO:6 or an empirical activity assay such that the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) could be applied to the polypeptide of SEQ ID NO:6. Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) compare amino acid sequences of polypeptides whose functions have been empirically characterized that are encoded by genes at *different* loci and suggest that 30 % sequence identity between polypeptides having the aforementioned characteristics, i.e., functional polypeptides encoded by genes at different loci, can be used to propose functional similarity of the polypeptides. However, Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) clearly DOES NOT suggest that *all* amino acid sequences with at least 40 % identity over 75 amino acids to another amino acid sequence will share a similar function. It is noted that, even assuming *arguendo* that the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) applied to all proteins – which they clearly do not – it is unclear as to the function that would be shared by the variants of SEQ ID NO:6 or a nucleic acid encoding therefor. As stated above, it is unclear from the specification as to the function of SEQ ID NO:6 and clearly, contrary to applicants' assertion, proteins that exhibit leucine-rich repeats do not share similar function as evidenced by Enkhbayar et al. (*Proteins* 54:394-403). Instead, Brenner (*Trends in Genetics* 15:132-133) discloses his opinion of functional prediction of a polypeptide *based solely on amino acid sequence* by teaching that it is impossible to know the accuracy of functional assignment without empirical laboratory evidence (page 132, left column, second paragraph), which it is noted, has not been provided in the specification. Also, it is well known in the art that highly homologous proteins can have distinct functions. As supporting evidence, the examiner provides the reference of Scott et al. (*Nat Genet* 21:440-443) who state that their result shows the importance of confirming the function of a protein even when the protein shares significant homology to proteins of known function (page 441, left column, third full paragraph). It is noted that applicant's claims are drawn to naturally occurring polynucleotides and polypeptides. The examiner provides the reference of Seffernick et al. (*J Bacteriol*

183:2405-2410) who teach two polypeptides having distinct functions that share 98% amino acid sequence identity (page 2407, right column, middle). While Seffernick et al. characterize their finding as "exceptional" (page 2409, left column, middle), this nonetheless provides evidence that polypeptides, even those sharing significant sequence identity, do not necessarily share function as asserted by applicant.

Applicants argue the state of the art at the time of the invention is further advanced than at the time of the *Lilly* and *Fiers* cases. Applicant argues the techniques and technological advances since the *Lilly* and *Fiers* cases up to the filing of the instant application in combination with the teachings provided in the instant specification are such that one of skill in the art would recognize that applicant was in possession of the claimed polynucleotides. Applicant's arguments are not found persuasive.

While advances in the art are undeniable and widely recognized, the rejection is directed to the lack of adequate written description and not lack of an enabling disclosure. Even with such advances, the state of the art still does not allow one of skill in the art to predict the structure and function of a naturally-occurring variant of a polypeptide based solely on a single disclosed amino acid sequence – see for example, Brenner (*Trends in Genetics* 15:132-133), Seffernick et al., and Scott et al. as described above. Most importantly, one skilled in the art would not be able to divine the function(s) of other naturally-occurring protein sequences based on the knowledge of the asserted (yet unconfirmed) function (whichever of hydrolase or phospholipase A2 inhibitory activity it may be) of only one disclosed species. For inventions in an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus.

[18] The enablement rejection of claims 21-30, 35-36, 41, and 43-45 under 35 U.S.C. 112, first paragraph is maintained for the reasons of record as set forth at item [13] of the Office action mailed September 23, 2003 and the reasons stated below. Applicants argue the claimed invention has a specific and substantial utility for those reasons presented at pages 11-29 of the amendment filed December 29, 2003. It is the examiner's position that the claimed sequences do not have a specific and substantial utility or a well-established utility for the reasons set forth in the rejection under 35 USC § 101 and

therefore are not enabled (see item [10] of the Office action mailed and item [15] of the instant Office action). Applicants' arguments traversing the instant rejection have been fully addressed above.

[19] Even if applicants demonstrate a specific and substantial utility for the claimed polynucleotide, polypeptide, and microarray, the scope of enablement rejection of claims 21, 23, 26-28, 30, 35, 41, and 43-45 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth at item [14] of the Office action mailed September 23, 2003 and the reasons stated below.

It is the examiner's position that the specification, while being enabling for a polynucleotide encoding SEQ ID NO:6 and a microarray comprising said polynucleotide and the polypeptide of SEQ ID NO:6, does not reasonably provide enablement for the entire scope of claimed polynucleotides, polypeptides, and microarrays. Applicants argue that one of skill in the art can readily identify the entire scope of claimed polynucleotide variants using known methods without undue experimentation. Applicants argue a skilled artisan would know how to use the entire scope of claimed variants. Applicants argue that one need only screen naturally occurring variants that have been determined through natural selection. Applicants argue the claims are drawn to polynucleotides and not polypeptides and it is the functionality of the polynucleotides that is relevant. Applicants argue that even nucleic acids encoding defective polypeptides may be useful. Applicants argue the examiner has failed to provide any reasons why one would doubt the guidance provided by the specification would enable one to make and use the claimed invention without undue experimentation according to the "standard" set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971) and *In re Borkowski,* 164 USPQ 642, 645 (CCPA 1970) and has not established a *prima facie* case of non-enablement. Applicant's arguments are not found persuasive.

Contrary to applicant's assertion, the examiner provided numerous reasons why applicant has not enabled the entire scope of claimed invention – see the analysis of the Factors of *In re Wands* 858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988) as set forth in item [14] of the Office action mailed September 23, 2003. While methods of isolating naturally-occurring variants of a given sequence are known in the art, *e.g.,* hybridization, the specification fails to provide guidance for using the entire scope of claimed nucleic acids. In this case, the claims encompass a broad scope of polypeptides and nucleic acids encoding polypeptides having *any* function. The specification fails to provide guidance for making and using these

variants. While applicants have limited the claims to naturally-occurring variants, applicants do not dispute the teachings of Seffernick et al. (*J Bacteriol* 183:2405-2410), which support the high degree of unpredictability that two naturally-occurring polypeptides will share similar function. Seffernick et al. teach two polypeptides that share 98% amino acid sequence identity (99% nucleic acid sequence identity) with distinct functions. This degree of unpredictability is greatly increased when one considers that the claimed variants broadly encompass those that are 90% identical to SEQ ID NO:6 or SEQ ID NO:22. This degree of unpredictability is even further compounded by the specification's confusing disclosure that SEQ ID NO:6 functions as a hydrolase and a hydrolase inhibitor. In this case, undue experimentation is required to screen all nucleic acids as encompassed by the claims for those that have the desired activity – whichever of hydrolase or phospholipase A2 inhibitory activity is intended for SEQ ID NO:6. Furthermore, contrary to applicants' assertion, the specification fails to provide guidance for using those polypeptides or polypeptides encoded by nucleic acids that are non-functional. While the claimed nucleic acid *may* useful in diagnosing one or more of the hundreds of diseases set forth in the specification, the specification fails to provide specific guidance for treating or diagnosing ANY specific disease. Thus, an undue amount of experimentation would be required to first determine whether any of the polynucleotide or polypeptide variants encompassed by the claims are causative or associated with any of the hundreds of diseases listed and further experimentation would be required to determine the steps required to diagnose or treat those disesase states – if any. In this case, applicants would require that a skilled artisan perform significant further experimentation without a particular direction to make and use the claimed variants. It is noted that nowhere does the examiner state that the claimed polynucleotide must encode a functional polypeptide. However, the specification clearly does not teach how a skilled artisan is use the entire scope of claimed polynucleotides, including those that encode non-functional polypeptides. Instead, the specification teaches only a single working example of the claimed polynucleotide – SEQ ID NO:22 and a single working example of the claimed polypeptide – SEQ ID NO:6. The specification provides no further guidance for using those polynucleotides that encode non-functional polypeptides or those polypeptides having function other than the asserted activity – whichever of hydrolase activity or phospholipase A2 inhibitor it may be. At most the specification provides a description that will enable a skilled artisan to

attempt to discover how to make and use the claimed invention and provides no more than a starting point for significant further experimentation (see *University of Rochester v. G.D. Searle & Co. Inc.,* W.D. N.Y., No. 00-CV-6161L, 3/5/03).

Claim Rejections - 35 USC § 102

[20] In view of the amendment to the claims filed December 29, 2003, the rejection of claims under 35 U.S.C. 102(a) and 35 USC 102(b) as set forth at items [16] and [17] of the Office action mailed September 23, 2003 are withdrawn.

Conclusion

[21] Status of the claims:

- Claims 21-30 and 32-45 are pending.
- Claims 32-34, 37-40, and 42-45 are withdrawn from consideration.
- Claims 21-30, 35-36, and 41 are rejected.
- No claim is in condition for allowance.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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